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IN THE

Supreme Court of the United States

OCTOBER TERM, 1966

No. 1044

JOHN C. KRANTZ, JR. and LOUISE SPEERS CROIX,
Petitioners,

v.

JOHN F. OLIN, *Respondent.*

PETITIONER'S REPLY BRIEF

On Petition for a Writ of Certiorari to the United States Court of Customs and Patent Appeals

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ARGUMENT IN ANSWER TO RESPONDENT'S BRIEF

A "sham" is defined as "a substitute, imitation, or counterfeit purporting to be the real thing."*

"Spurious" means "not genuine, counterfeit, false."*

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* Webster's New International Dictionary, Second Edition (1953).

When Olin filed his patent application on December 29, 1955 he had no practical use, no utility, for his new compound. All he had was the Latven letter of August 9, 1955 (Olin Exhibit P, reproduced in Petitioners' Brief at pages 42a and 43a, Appendix VI) reporting the results of the tests of the new compound for its originally hoped-for use, as an anesthetic.

Not having any real or true utility, Olin included in his application a sham utility, one that looked like an actual and practical utility and was disclosed in a manner which would lead the Patent Examiner so to think. It was mere speculation presented in the guise of fact. It was completely unsupported by experimental evidence of any kind. In fact, the experimental evidence then available to Olin was to the contrary; Latven had reported to Respondent that the compound was "extremely toxic and is absorbed systematically within seconds following inhalation." Olin's disclosure of utility was a substitute, an imitation, a counterfeit purporting to be the real thing. It was misleading in two respects, (1) in what it said or implied that was not true and (2) in what it omitted that was known to Olin and would have been material and essential to one attempting to use the new compound for the purposes alleged in the Olin application. It was a sham.

Respondent's Brief attempts to perpetuate this sham by asserting that certain parts of the experimental work done by Petitioners for the purpose of this case, as reported in the affidavits of Petitioners' experts, Neeley and Wamser, show that there was some truth in the utility allegations made in the Olin application. This attempt should fail. True, the Wamser

and Neeley affidavits show that some solvent properties were present. Any liquid has some solvent action, but the affidavits of both these witnesses when considered as a whole show that the new compound would not be practically useful as a solvent. They prove that the solvent utilities alleged in the Olin disclosure are *not* real or genuine, but rather are spurious, mere shams or substitutes purporting to be a real thing.

Who would use as a solvent a compound having the toxic properties reported to Respondent in Latven's August 9, 1955 letter? Wamser and Neeley say no one would, as a practical matter. The record shows that the only known use is as a drug (following years of clinical testing by Petitioners), and the Federal Food and Drug Administration restricts such drug use only to competent physicians, as shown in the following excerpt from the instructions for use* shipped with each quantity of the drug:

> *Contraindications*
>
> Contraindications for Indoklon are similar to those for electroshock therapy. Indoklon should not be given to a patient with even a very mild upper respiratory infection. Indoklon should not be given to any patient with severe cardiovascular, hepatic, or renal disease. Indoklon should not be given to any patient with severe intraocular or intraspinal increase in pressure. Patients with abnormal body temperatures should be temporarily excluded from Indoklon therapy until the temperature returns to normal. Indoklon is not to be used with pregnant females, since no data is available to support its safe use in pregnancy.

---

* A complete copy of these instructions is reproduced in the Appendix to this Reply Brief.

Precautions

Indoklon should be administered by a competent physician who is familiar with simple resuscitative procedure. It is recommended that it be administered in a hospital, or other place of treatment where restorative drugs, oxygen and resuscitation equipment are available. The legal formalities to be observed are identical with those employed in the administration of electroshock therapy, insulin coma therapy, or other similar types of psychiatric therapeutic treatments.

Respondent further attempts to prove the practicality of the alleged solvent utility of the new compound (in the absence of any experimental work by Respondent whatsoever) by comparing the new compound with the solvents listed as "definitely hazardous" in Chapter 2 relating to Safe Practices in the Handbook of Solvents. But the comparison falls short. Common, well-known substances such as benzene, methyl alcohol and carbon tetrachloride (listed as *definitely hazardous* in the Handbook) are not in the same category with respect to toxicity, or physiological effect, as the new compound of the Olin application. Olin knew when he filed his application that as little as .0051 cc/liter would cause severe muscular spasms in mice. He knew that his investigator Latven urged him to "AVOID ACCIDENTAL INHALATION AT ALL COSTS." At the very least he had the obligation, not only in the public interest but also to meet the requirements of 35 U.S.C. § 112, to include such essential information in his patent application. And it is no excuse to say (as Respondent suggests) that Latven was talking about mice, not men. It is simply incredible that Latven, when he imagined what might happen if a glass container of the new compound were accidentally broken by being dropped on the floor (Olin

Exhibit P) was concerned not about the human hazards involved but rather about the possibility that mice in the laboratory might be killed.

The situation here might be likened to a case wherein a patent application were filed on an explosive liquid such as nitro-glycerine based on the alleged utility of the liquid as a solvent and as a chemical intermediate, but completely omitting the essential information about the explosive qualities of the liquid. Any such patent application clearly would be "fatally" deficient in disclosure. So too is the case with respect to the subject Olin application.

CONCLUSION

Certiorari should be granted for the reasons stated in the Petition which Respondent's Brief, properly understood, demonstrates rather than refutes.

Respectfully submitted,

W. Brown Morton, Jr.,
and
H. Hume Mathews,
Attorneys for Petitioners.

Melford F. Tietze,
Of Counsel.

March 16, 1967

INDOKLON®

FLUROTHYL

(Bis(2,2,2-trifluoroethyl)ether)

A CONVULSANT AGENT FOR PSYCHIATRIC USE

A recent revival in pharmacologic convulsive therapy has been achieved through the discovery that seizures can be safely induced with the drug Indoklon, bis(2,2,2-trifluoroethyl)ether. The use of this ether for the treatment of psychiatric patients in whom convulsive therapy is indicated was first suggested when it was found that Indoklon evoked a convulsive action upon inhalation by laboratory animals. A subsequent comprehensive clinical evaluation demonstrated its usefulness as a safe agent for treatment of mental illness in man.[1]

The drug is administered by inhalation. The seizures are similar to convulsions elicited by electro-shock; but their onset is more gradual. It appears that the seizures are similar to those achieved by other convulsive techniques except that with Indoklon the clonic phase tends to last longer. However, at a cellular level the mechanism of the seizure as in other techniques has not been completely delineated. Indoklon is unique among the pharmacological agents commonly used to induce seizures since it is eliminated through the lungs.

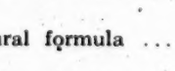
PHYSICAL PROPERTIES[2]

Indoklon is an ether and from a structural point of view it is considered to be a fluorinated derivative of diethyl ether. It is known chemically as bis(2,2,2-trifluoroethyl)ether; it is sometimes referred to as hexafluorodiethyl ether.

Indoklon is a colorless volatile liquid having a pleasant ethereal odor. By vapor fractrometry analysis it has a purity of 99.6% or higher. No stabilizers are added. Its boiling point is 63.9°C and its specific gravity is 1.417 at 20°C. It is slightly soluble (0.2%) in water, but dissolves readily in ethyl alcohol and polyethylene glycol 300. Indoklon has an oil-water coefficient of 116. It is possible that this property is associated with its distribution in the brain and hence responsible for its stimulating effect.

Since Indoklon has a flash point of 104°F, by the "Tag Open Cup" method, it falls into the category of a combustible liquid as defined by the Manufacturing Chemists' Association code. Its vapor has a lower limit of flammability of 7% in dry oxygen and approximately 20% in dry air.

The physical properties of Indoklon are summarized in the following table:

Structural formula		
Molecular weight	182.07	
Boiling point	63.9°C/760 mm.	
Freezing point	Below -80°C	
Refractive index	1.2797	$20^{\circ}C$
Specific gravity	1.417	$\frac{20}{20}$
Weight per gallon	11.79 lbs.	20°C
Flash point, Tag Open Cup	Approx. 40°C (104°F)	
Vapor pressure	168 mm	20°C
	292 mm	35°C
	504 mm	50°C
	760 mm	63.9°C
Solubility in water	0.2% by weight	
Solubility of water in Indoklon	<0.1% by weight	

CHEMICAL PROPERTIES

Indoklon is an extremely stable organic ether. Unlike other ordinary ethers it does not undergo cleavage when treated with hydriodic acid and cannot be oxidized by the action of strongly acidified potassium dichromate solutions. In fact, no chemical reactions have been found that can be used as the basis of a method for the chemical assay of the drug. This extreme stability of Indoklon necessitates the utilization of purely physical methods in the analysis of mixtures for the identification and determination of the compound.

ANIMAL EXPERIMENTATION

The first demonstration that Indoklon would cause convulsions was carried out on rats by Dr. John C. Krantz, Jr., of the University of Maryland, School of Medicine.[3] He observed that all species of animals exposed to Indoklon vapors convulsed with great rapidity. There seemed to be little species difference in the susceptibility or tolerance toward Indoklon in the dog, monkey, mouse or rabbit. It was subsequently determined that animal dosage levels could be extrapolated to man with negligible variation. It is remarkable that Indoklon evokes seizures in rats at concentrations as low as 30 ppm (wt./vol.) within 30 seconds. The Indoklon seizure is compatible with the administration of atropine sulfate, thiopental sodium and succinylcholine chloride.[4]

The cortical dysrhythmia evoked by Indoklon in the monkey can be blocked by placing the animal under the deeper planes of ether, Fluoromar or thiopental sodium anesthesia.[5]

The previous administration of reserpine lowers the threshold of the Indoklon seizure similar to that observed with electroshock therapy. The antipsychotic drugs of the phenothiazine series, e.g. chlorpromazine, also lower the threshold to electroshock or Indoklon convulsions.[4]

In addition to the foregoing studies, carried out at the University of Maryland, several studies at the University[6, 7] of Wisconsin were conducted on Sprague Dawley rats and mongrel dogs. In the more extensive tests, dogs from the same litter were selected. To determine if pathologic changes could be produced, members of each of these species were subjected to tests involving increase in the number or the duration that might be administered clinically. The tests were conducted in two series: In the first series Sprague Dawley rats and mongrel dogs were subjected to a ten to twenty fold increase in the number or the duration of convulsions as compared to the number or the duration that might be administered clinically.

Convulsions occurred in the dog after one inhalation and following one or two blood circulation times. Convulsions were produced 25 or more times in 4 animals. Indoklon was administered 3 or 4 times for 30-minute periods to 7 other dogs. The only pathologic changes noted in the study of these animals were: one instance of focal liver necrosis, one of periductule lymphocytic infiltration of the liver, and one of a fatty liver. Such changes could result from inadequate pulmonary ventilation and carbon dioxide accumulation. There were no significant changes in blood sodium, potassium or calcium levels.

Electroencephalographic changes were studied in dogs and consisted of maximal seizure patterns. Electrocardiograms revealed A-V nodal dissociation, ventricular extrasystoles, complete heart block and bigeminal rhythm. All arrhythmias returned to normal at the end of the treatment period. These changes are similar to those observed with other methods of convulsion therapy.

In the second comprehensive series of tests, 5 dogs were each given 100 successive treatments in dosages adequate to produce grand mal type of seizures as seen visually and recorded electroencephalographically. This was an increase of approximately 85 to 90 over the number that might be administered clinically. In this series of experiments pathologic changes also were shown to be minimal as evidenced by the examination of microscopic sections of the following from each of the 5 dogs: liver, spleen, kidney, adrenal, small intestine, ovary or testis, lungs and both right and left ventricular walls.

CLINICAL PHARMACOLOGY

Indoklon has been studied in various clinics in the United States and abroad since 1957. The greatest therapeutic success has been achieved with depressed psychotic patients. Combined therapy with EST treatment and Indoklon on the same patient has not yet been adequately explored. From the data available, it is abundantly clear that Indoklon convulsive therapy offers an effective alternate treatment to EST in many patients.[9, 10, 11, 12, 13, 14]

As with EST, the muscular component of the seizures induced by Indoklon can be markedly mitigated by the previous injection of succinylcholine chloride (Anectine). Many clinics have confirmed the results obtained at the Spring Grove State Hospital,[9] Baltimore, Maryland, in studies on 60 patients given electroshock treatment and approximately the same number of patients given Indoklon treatments. All patients were screened physically and considered free from complicating medical disorders before treatment. The screening process consisted of a physical examination, X-ray of the chest and spine, electrocardiogram, routine urine, blood chemistry, hemotologic tests, and liver function tests consisting of cephalin flocculation and thymol turbidity. In the Indoklon group 720 treatments were given to the 60 patients and approximately the same number of treatments given in the EST series. Clinical observation at present indicates that there appear to be no differences in the clinical courses of either group of patients. The quantity of Indoklon needed to produce a convulsion by the inhalation technique averaged 0.5 ml. Tolerance was not noted with progressive treatments. Spasmodic clonic episodes with some degree of laryn-

pleasant ethereal odor. By vapor fractrometry analysis it has a purity of 99.6% or higher. No stabilizers are added. Its boiling point is 63.9°C and its specific gravity is 1.417 at 20°C. It is slightly soluble (0.2%) in water, but dissolves readily in ethyl alcohol and polyethylene glycol 300. Indoklon has an oil-water coefficient of 116. It is possible that this property is associated with its distribution in the brain and hence responsible for its stimulating effect.

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Repeated convulsions on subsequent days in dogs did not produce harmful effects. This was demonstrated by histologic studies of the lungs, brain, liver, kidney and bone marrow. Tolerance to the agent does not develop when rats are subjected to Indoklon seizures daily over 14 days. The convulsions are not mediated through hypoglycemic shock or the inactivation of cholinesterase. Electroencephalographic studies in monkeys and dogs with thiopental sodium anesthesia and muscle relaxation provided by succinylcholine chloride showed marked cortical dysrhythmias without skeletal muscle involvement. The multiple spike and the 3 to 4 second slow wave discharge that occurred first are followed rapidly by high voltage multiple spiking similar to that of monoclonic type (petit mal) epilepsy. Upon the elimination of Indoklon, the EEG pattern returned rapidly to normal.

Studies in dogs and monkeys show that the Indoklon seizure does not adversely affect the electrocardiogram. The blood pressure falls slightly during the seizure (10 to 15 mm.), but returns rapidly to normal with recovery. Indoklon vapors evoke only a slight irritation to mucous membranes. Mild chemosis of the conjunctiva of the rabbit is evoked when Indoklon dissolved in oil is instilled in the rabbit's eye. In a comparative study the degree and duration of the Indoklon chemosis was found to be not greater than that elicited by ethyl ether.

Indoklon is a respiratory stimulant in subconvulsive doses. This action is principally central in origin, rather than a reflex response from the pharyngeal region which prevails upon ether inhalation. Metabolism studies were conducted on rat's brain hemogenates. Prior to and immediately following Indoklon-induced convulsion, the oxygen uptake of the rat's brain was determined by the Warburg technique. No statistically significant differences were noted. This indicates that single exposures to Indoklon do not irreversibly affect the gaseous metabolism of the brain.

Experiment on dogs and monkeys and clinical trials with human beings have shown that the [illegible] times. Convulsions were produced 25 or more times in 4 animals. Indoklon was administered 3 or 4 times for 30-minute periods to 7 other dogs. The only pathologic changes noted in the study of these animals were: one instance of focal liver necrosis, one of periductule lymphocytic infiltration of the liver, and one of a fatty liver. Such changes could result from inadequate pulmonary ventilation and carbon dioxide accumulation. There were no significant changes in blood sodium, potassium or calcium levels.

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Electrocardiograph tracings obtained from patients before and during seizures with Indoklon were compared with a group of tracings obtained from the electroshock patients.[12] There were no significant differences. Routine blood and urine examinations have remained consistently negative. The cephalin flocculation and thymol turbidity tests for liver function showed no changes from the base line following Indoklon therapy.

A group of 33 patients (27 women and 6 men) was studied for a period up to 14 months.[13] Their ages ranged from 21 to 65 years. The majority were between the ages of 30 and 50. The average number of treatments given to each patient was 12. A total of 409 treatments were given, 220 of which were given to ambulatory patients. It was found that the patients preferred outpatient treatments to intramural treatments, and whenever possible, this preference should be taken into consideration. In cases of lack of reliable supervision of the patient in the period between treatments, hospitalization of the patients is mandatory.

A series of experiments were run to determine the manner in which Indoklon is eliminated from the body. It was found in 8 determinations[14] that approximately 50% of the drug, injected in a single treatment, was eliminated unchanged through the respiratory system in 30 minutes. The experiments were not carried for a longer time since it was undesirable to carry these patients under anesthesia for a longer period of time. It is believed, however, that due to the extreme chemical stability of Indoklon, the remainder of the drug is eliminated in the same manner following the initial 30 minute period.

ADMINISTRATION BY INHALATION[14, 15, 16, 8]

The pure Indoklon is supplied in 2 cc and 10 cc ampules, packaged six ampules to a box. For administration, a 5-liter bag attached to the oxygen supply is connected to the Indoklon vaporizer. The vaporizer is, in turn, connected to the face mask. Two ml. of Indoklon are introduced into the vaporizer and the bag is partially inflated with oxygen. The connection to the oxygen supply is maintained during inflation. Some examiners give the Indoklon without other premedication.[11] For those who wish, the following technique of premedication can be used but is not essential. A volume of atropine sulfate solution equivalent to 1/75 grain of (0.8 mg) is injected intravenously through a 22-gauge needle. By leaving the needle *in situ*, the syringe containing the atropine is removed and a syringe containing 10 cc of a 1% solution of methohexital (Brevital sodium) is connected to the needle in the vein. Eight to 10 ml. of this solution are usually adequate to anesthetize the patient for a few minutes. The methohexital syringe is removed and a syringe containing succinylcholine chloride (Anectine) is attached and the drug administered immediately. The amount used depends on the muscular development of the patient and may vary from 15 to 20 mg. for a woman of average weight to 20 to 40 mg. for an average weight man. In exceptional cases a larger amount may be required.

An adult rubber Guedel oral pharyngeal airway is then inserted. The face mask is placed tightly on the face and the bag is gently squeezed, forcing the oxygen-Indoklon mixture into the lungs at the rate of one inhalation every five seconds. The patient rebreathes into the bag. The usual number of inhalations required to cause convulsions may vary from four to six. Only rarely is it necessary to refill the bag with oxygen. The seizure usually occurs within 40 seconds, thus utilizing the maximal effect of succinylcholine chloride. The onset of the seizure depends upon the blood circulation time and the time required for the maximum Indoklon effect. This is usually less than 1 minute. The tonic phase of the seizure is over in ten to thirty seconds, but the clonic phase lasts for approximately 1 minute. In almost all patients respiration starts at the termination of the clonic phase. No period of apnea, as seen almost routinely in electroshock therapy, has been noted with Indoklon.

In a certain series, two patients, one of whom was an epileptic, had a second convulsion immediately after the termination of the first. This can be avoided by administration of the minimal amount of Indoklon necessary to produce a seizure.

Since the patient is resuscitated during the administration of the drug, some investigators have found it unnecessary to continue this treatment following the seizure. Others continue resuscitation until the effects of the succinylcholine chloride have completely disappeared.

Nevertheless, it is recommended that equipment for administration of oxygen resuscitation be available should this treatment be necessary, in cases of collapse and respiratory failure.

The inhalation method has the advantage of facilitating control of the amount of oxygen mixed with the Indoklon vapor. At the same time, the manual pressure on the oxygen-filled bag permits the Indoklon vapor to be forced into the lungs of the anesthetized patients without over-saturating them. This technique ensures proper timing of the convulsion, and enables the patient to benefit from the mitigating effect of succinylcholine chloride. It is important not to use too much oxygen because excess oxygen in the Indoklon mixture delays the onset of the convulsion resulting in a loss of effect from the muscle-relaxing agent.

It has been noted that many patients who object strongly to electroshock therapy accept Indoklon because of the assurance that no electricity will be used during the course of these treatments. It is, of course, also true that some patients who object to Indoklon accept electroconvulsive therapy. This is a matter which has to be worked out between the physician and his patient.

The procedure is simple and safe. The presence of an anesthesiologist is not essential for the proper administration of Indoklon.

COMPATABILITIES AND INCOMPATABILITIES

No known incompatabilities with Indoklon have been reported. Antidotal studies in rats were conducted to attempt to combat the convulsive syndrome. In 6 animals 30 mg./kg. of pentobarbital sodium injected intraperitoneally prior to exposure provided complete protection against a concentration of 30 ppm of Indoklon. Thiopental sodium likewise afforded protection in 4 animals. Ether anesthesia prevented the convulsive syndrome in 4 animals, and Fluoromar® anesthesia was likewise effective in 4 animals.

CONTRAINDICATIONS

Contraindications for Indoklon are similar to those for electroshock therapy. Indoklon should not be given to a patient with even a very mild upper respiratory infection. Indoklon should not be given to any patient with severe cardiovascular, hepatic, or renal disease. Indoklon should not be given to any patient with severe intraocular or intraspinal increase in pressure. Patients with abnormal body temperatures should be temporarily excluded from Indoklon therapy until the temperature returns to normal. Indoklon is not to be used with pregnant females, since no data is available to support its safe use in pregnancy.

PRECAUTIONS

Indoklon should be administered by a competent physician who is familiar with simple resuscitative procedure. It is recommended that it be administered in a hospital, or other place of treatment where restorative drugs, oxygen and resuscitation equipment are available. The legal formalities to be observed are identical with those employed in the administration of electroshock therapy, insulin coma therapy, or other similar types of psychiatric therapeutic treatments.

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